between the said probe and amplified sequences of nucleic acids; and

(4) detecting any first hybridization complexes present; and

(5) determining if said first hybridization complexes are also capable of forming second hybridization complexes with a nucleotide probe for detection of specific sequences of nucleic acids of M. tuberculosis complex other than BCG comprising a sequence of the region of sequence SEQ ID No: 2 comprising the GAG codon in positions 40 to 42 or its complementary strand, the presence of said second hybridization complexes being indicative of the presence of a M. tuberculosis strain different from BCG.

REMARKS

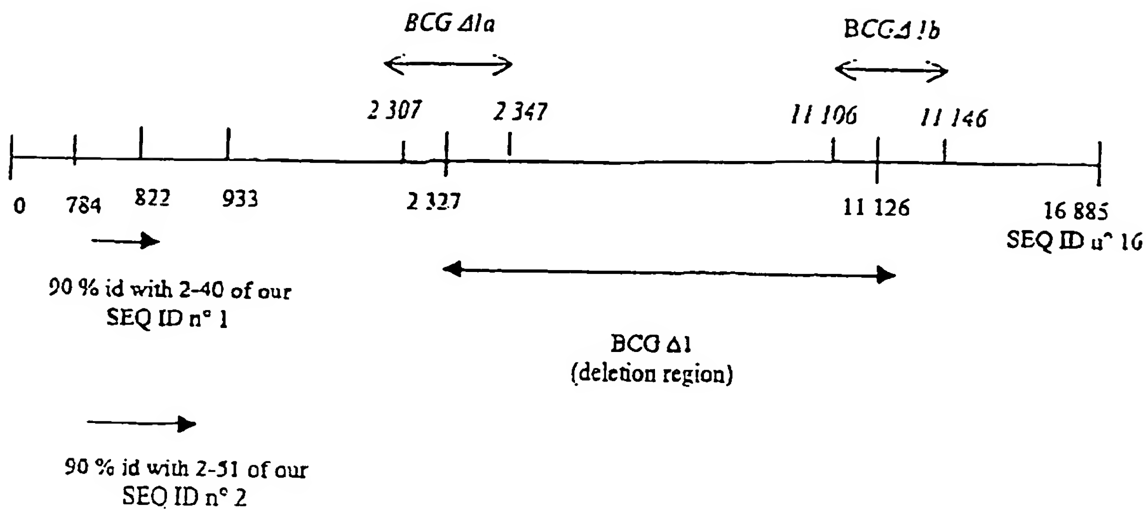
The amendment is presented to insert reference to the parent applications, amend the specification as in the parent application and to rewrite all the claims to avoid the objections to the claims as last filed therein.

In the parent application, Claims 28 to 31, 33, 34, 37 to 39, 41 to 43, 45 to 47, 49, 50 and 53 were rejected under 35 USC 102 as being anticipated by the Stover et al patent. Claims 51, 52 and 55 were rejected under 35 USC 103 as being obvious over the Stover et al patent taken in view of the Van Embden et al reference. Claims 23, 24 and 27 remain rejected over Stover et al in view of Van Embden et al. The Examiner states that the Stover et al patent teaches fragments of

nucleic acids that are capable of hybridizing to SEQ ID No: 1 and No: 2 and the compliments of the said sequence ID numbers under conditions of high stringency as defined in the specification. Many of the Stover et al sequences would reasonably be expected to meet the limitations of the present claims according to the Examiner.

Applicants respectfully traverse these grounds of rejection since Stover et al, taken alone or in view of the secondary art, does not anticipate or render obvious Applicants' invention which relates to the nucleic SEQ ID No: 1 and No: 2 which permits differentiation of BCG from other bacteria of the M. tuberculosis complex. With respect to the Examiner's allegation that Stover et al discloses deleted regions in the BCG genome and that these deleted regions are indicative of an avirulent phenotype, this objection is now moot since amended claims 28 to 30 no longer call for the hybridizing sequences. Moreover, the sequences or probes that can be derived from the SEQ ID No: 16 of Stover et al do not anticipate the probes or primers of the present application.

The Examiner's analysis of the Stover et al patent is apparently effected by several misunderstandings. The teaching of Stover et al can be summarized by the following scheme:



According to Stover et al, the markers or probes that can be derived from the SEQ ID No: 16 of Stover et al may be a) the full length BCGΔ1a or BCGΔ1b or a sequence within these regions as taught in line 67 of column 1 and lines 1 and 3 of column 2 or a sequence selected from an open reading frame (ORF) of the BCGΔ1 deletion sequence (see lines 9 and 10 of column 2), the BCGΔ1 ORFs are depicted in Figure 4.

The nucleotide sequences 784-933 of SEQ ID No: 16 which shows 90% identity with nucleotides 2 to 40 of SEQ ID No: 1 of the present application neither belongs to BCGΔ1a or BCGΔ1b nor to BCGΔ1 and thus, cannot be a marker sequence according to Stover et al. Moreover, if one refers to the general characterization of the sequences according to Stover et al, it is specified that the sequences are either deletion junction sequences or deletion sequences or subsequences within these sequences (lines 50 to 53 of

column 1). A definition of "deletion junction" is recited beginning at line 62 of column 4, it is mentioned that a sequence spans to nucleotides that are immediately adjacent to the deletion sequence. In no event can the Examiner maintain that the nucleotides lined between position 784 to 933 are immediately adjacent to nucleotide 2327 of SEQ ID No: 16.

Moreover, Applicants wish to stress that the specification states that "A probe will be selected that hybridizes to the target junction sequences (i.e. BCGΔ1a and BCGΔ1b) or deletion sequences [i.e. BCGΔ1] but not to other microbacterial nucleic sequences under stringent conditions" in lines 37 to 40 of column 12. Within the context of Stover et al, the nucleic acid fragment 784-933 is another microbacterial nucleic acid since this fragment shows no homology to BCGΔ1a, BCGΔ1b or BCGΔ. A probe according to Stover et al is preferably 17 to 25 base in length (see line 59 of column 12). Therefore, a probe comprising the fragment 784-933 would be at least 1,543 bases long, i.e. ranging from nucleotide 784-2327 which is a 100 fold increase as compared to the mentioned length. Therefore, Stover et al does not anticipate or render obvious Applicants' invention.

Stover et al contains no incentive to try and detect a deleted region different from BCGΔ1, BCGΔ12 or BCGΔ3. Therefore, Applicants' invention has an inventive step over Stover et al. The obviousness rejection is deemed to be moot since Van Embden et al

does not teach that a BCG strain can be detected from other M. tuberculosis complex strains by detecting a deletion of nucleotides 40 to 60 in the intercistronic region repeated SEQ ID NO: 1. Therefore, one skilled in the art would not have been led to Applicants' invention by combining the two documents. Therefore, withdrawal of these grounds of rejection is requested.

In view of the proposed amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable consideration of the application is requested.

Respectfully submitted,
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